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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

GUENTER KNAUP, ET AL. : EXAMINER: KIM, S. U.

SERIAL NO: 09/769,397 :

FILED: JANUARY 26, 2001 : GROUP ART UNIT: 1723

FOR: AMINO ACID COMPOSITION FOR HEMODIALYSIS :

DECLARATION UNDER 37 C.F.R. §1.132

ASSISTANT COMMISSIONER FOR PATENTS
ALEXANDRIA, VA 22313

SIR:

Now comes Professor Adolf Grünert who deposes and states that:

(1) I am the Medical Director and Chairman, Institute of Clinical Chemistry, University Hospital, Robert Koch-Str. 8, D-89070 Ulm in Germany.

(2) A copy of my Curriculum Vitae is attached hereto.

(3) I am an inventor in the present application.

(4) I understand the English language or, at least, that the contents of this Declaration were made clear to me prior to executing the same.

(5) The field of the invention of the present application is compositions suitable for hemodialysis.

(6) Based on my years of experience working in the field of the invention, I consider myself an expert in that field.

(7) I have read and am familiar with the present application, including the claims of that application.

(8) I have read and am familiar with the Official Action dated December 17, 2002 in the present application.

(9) I have read and am familiar with Quarto di Palo et al., The International Journal of Artificial Organs, Vol. 1, No. 1, 1978, pp. 112-113, cited in the Official Action dated December 22, 2002.

(10) At page 112, column 2, lines 9-11 of text under "Sir," Quarto di Palo et al. state:

> we have tried adding amino acids to the dialysis solution in a concentration equal to that of normal plasma.

(11) The dialysis solution described by Quarto di Palo et al. does not contain the complete pattern of amino acids present in normal plasma. The dialysis solution described by Quarto di Palo et al. is missing Gln, Tyr, Cys, Asn, and Cit, all of which are present in normal plasma.

(12) In 1978, when Quarto di Palo et al. was published in the scientific literature, the complete amino acid composition of normal plasma was well-known in the art. That this is so is demonstrated by Meister, A. (ed.), Biochemistry of the Amino Acids, Second Edition, Vol. 1, pp. 110 (1965). A copy of pages 108-117 of that reference text is attached hereto.

(13) In addition, the Table at the top of page 113 of Quarto di Palo et al. explicitly stated that Cit (citrulline), Cys (cystine), and Tyr (tyrosine) are present in normal plasma at a specified range, but are not present in the dialysis solution described in that reference.

(14) At the time the present application was filed in 1999, one of ordinary skill in the field of the invention would have interpreted Quarto di Palo et al. to suggest that if an

amino acid is used in the dialysis solution, then it should be used at a concentration in the range for normal plasma.

(15) Significantly, however, since the amino acids Gln, Tyr, Cys, Asn, and Cit were not used by Quarto di Palo et al., and those amino acids were well-known as components of normal plasma at the time that reference was published, one of ordinary skill in the field of the invention reading that reference at the time the present application was filed in 1999 would have concluded that Quarto di Palo et al. did not consider those amino acids to be useful components of a dialysis solution, even though they were known components of normal plasma. Otherwise, Quarto di Palo et al. would have used those amino acids in the dialysis solution described in that reference.

(16) In view of the foregoing, Quarto di Palo et al. would not have suggested to one of ordinary skill in the art in the field of the invention at the time the present application was filed in 1999 to modify the dialysis solution described by Quarto di Palo et al. by including Gln, Tyr, Cys, Asn, and Cit. This is because one skilled in the art would have recognized in 1999 that if Quarto di Palo et al. considered those amino acids to be useful components of a dialysis solution, then Quarto di Palo et al. would have included them in the dialysis solution described in that reference. Since those amino acids were well-known components of normal plasma in 1978 at the time that the Quarto di Palo et al. reference was published, the fact that Quarto di Palo et al. failed to use Gln, Tyr, Cys, Asn, and Cit would have been considered one of ordinary skill in the art in the field of the invention at the time the present application was filed in 1999 as a direct teaching away from the dialysis composition claimed in the present application.

(17) As described in the specification of the present application at pages 1-2, patients with impaired kidney function have imbalanced amino acid compositions.

(18) As noted above, the dialysis solution described by Quarto di Palo et al. is based on the amino acid content of normal plasma.

(19) However, as described in the specification of the present application at page 2, administering such a solution to the patient actually exacerbates the amino acid imbalance in the patients. As a result, the dialysis method like that described by Quarto di Palo et al. has not been adopted for routine therapy, and has been evaluated as too expensive and ineffective. That this is so is demonstrated by Tepper et al., The International Journal of Artificial Organs, Vol. 1, No. 4, 1981, pp. 208-210, a copy of which is submitted hereiwth.

(20) The dialysis solution described by Quarto di Palo et al. has the following disadvantages as compared to the dialysis composition claimed in the present application:

(a) the total concentration of the dialysis solution described by Quarto di Palo et al. is with 250 mg/L not sufficient to compensate for the concentration gradient of amino acids, and

(b) the total concentration with 407 mg/L of the composition claimed in the present application is isotonic with respect to plasma amino acid concentrations in healthy people. See Grünert et al., Infusiontherapie, 11, 12-15 (1984) and Grünert et al., Anaesthesist, 33, 11-19 (1984), copies of which are submitted herewith.

(21) The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both,

under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

(22). Further deponent saith not.

Professor Adolf Grünert

06-12-2003
Date

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